

## Description

### EXTENDED-RELEASE TABLETS OF METFORMIN

#### Technical Field of the Invention

[1] The present invention relates to extended-release unit dosage formulations of metformin or its pharmaceutically acceptable salt thereof and the process for their preparation.

#### Background of the Invention

[2] Extended-release pharmaceutical dosage forms have received much attention in recent years and are highly desirable for providing a constant level of pharmaceutical agent to a patient. The nature of the delivery system is dictated by the properties and dose of the drug, desired release profile and physiological factors. For example, it is challenging to develop an extended-release system for a high dose, water-soluble drug with a narrow absorption window limited to either stomach and/or the upper intestine.

[3] Extended-release dosage forms not only increase patient compliance due to reduction in frequency of dosing, but they also reduce the severity and frequency of side-effects, as they maintain substantially constant blood levels and avoid fluctuations associated with the conventional immediate release formulations.

[4] Metformin has been widely prescribed for lowering blood glucose in patients with non-insulin dependent diabetes mellitus (NIDDM). However, being a short acting drug, metformin requires twice (bid) or three times-a-day (tid) dosing. A clear advantage of an extended-release dosage form would be a reduction in the frequency of administration.

[5] Adverse events associated with metformin use are often gastrointestinal, e.g. anorexia, nausea, vomiting and occasionally diarrhea, etc. These adverse effects may be partially avoided by reducing the initial and/or maintenance dose or using an extended-release dosage form.

[6] Metformin has intrinsically poor permeability in the lower portion of the gastrointestinal tract, leading to absorption from the upper part of the tract. It has very high solubility in water (>300mg/ml at 25°C). These parameters can lead to difficulty in providing a sustained release of the drug from a formulation and the concomitant problems associated with controlling the initial burst from such a formulation. The rate of dissolution of such high solubility drugs may be reduced by embedding the drug in a polymeric matrix or surrounding it with a polymeric barrier membrane through which the drug must diffuse to be released for absorption.

[7] The approaches may be beneficial for low dose drugs as large amounts of polymers are required but not for those drugs that are administered in daily doses of the order of many hundreds of milligrams.

[8] Metformin hydrochloride is commercially available under the brand name Glucophage® (conventional) and Glucophage XR (extended-release tablets), currently

marketed by Bristol Myers Squibb. Glucophage conventional tablets contain 500 mg, 850 mg and 1000 mg of metformin hydrochloride. Glucophage XR tablets (500 mg metformin hydrochloride; extended-release) comprise a dual hydrophilic matrix system which is described in U.S. Patent 6,475,521, which relates to a method for preparing a biphasic controlled release delivery system adapted for delivery of metformin. It describes a two phase system which includes an inner solid particulate phase containing the drug and an extended-release material and an outer solid continuous phase containing extended-release material. On coming in contact with the release medium, the drug released from the particles of the inner phase, migrates through the outer solid continuous phase and is then released into the upper gastrointestinal tract.

[9] However, the total tablet weight of each tablet containing 500mg of the active ingredient is about 1000 mg, as substantial amounts of polymers are required for controlling the rate of drug release. A scale-up formulation containing 1000mg drug, when made according to this invention would weigh at least 2 g. This would be unacceptably large for human consumption, and two tablets of 500mg strength each would be required for administering the daily adult dose of 1000mg metformin.

[10] Metformin is a highly water soluble drug having poor flow and compressibility characteristics, hence, cannot be compressed in its pure form. Moreover, it is a high dose drug and therefore the tendency for capping is particularly high during the production of tablets. This capping results not only in loss of yield but also impairment of the quality. The high drug content does not allow much variation in the amount of excipients.

[11] Attempts have been made to obtain directly compressed tablets by compressing drug and suitable excipients, which can aid in processing and improve the properties of the product. However, direct compression is usually limited to those situations where the drug has a crystalline structure and physical characteristics suitable to form pharmaceutically acceptable tablets. But, in cases where the active ingredient is not compressible directly, one or more excipients must be added. Since each excipient added to the formulation necessarily increases the tablet size, direct compression method is practically limited to formulations containing a low-dose active ingredient. Moreover, the tendency for capping is particularly high in case of directly compressed tablets containing high doses of active ingredient.

[12] One such attempt was made in U.S. Patent No. 6,117,451 which describes the use of specific excipients of particular size and density range to improve the flow and compressibility of metformin hydrochloride. These excipients are blended with metformin and the blend is then directly compressed. In this patent, the wet granulation method is used to convert a powder mixture into granules having suitable flow and cohesive properties for tabletting. The process involves mixing the powders in a suitable blender followed by adding the granulating fluid under shear to the mixed powders to obtain a

granulation. The damp mass is then screened through a suitable screen and dried. The wet granulation process may also result in variable release characteristics depending on the degree of hydration of the polymer. Even the fluid volume of the granulating agent and granulating time may also affect the release characteristics. Further, use of organic solvent leads to issues of residual solvent.

- [13] U.S. Patent No. 5,955,106 discloses a process comprising granulating metformin and a hydrocolloid-forming retarding agent with an aqueous solvent to form a granulated product and drying the granulated product. The hydrocolloid-forming agents, on coming in contact with aqueous medium, swell and form a gel matrix which erodes to release the drug.
- [14] Extended-release compositions of metformin have also been formulated using other techniques. U.S. Patent No. 6,340,475 describes oral dosage forms in which the drugs are incorporated into polymeric matrices comprised of hydrophilic polymers that swell upon uptake of water to a size that is large enough to promote retention of the dosage form in the stomach. The swollen polymeric matrix remains intact long enough for substantially all of the drug to be released before dissolution of the matrix occurs.
- [15] However, there is still a need for a dosage form for metformin, which is capable of incorporating a high dose, is simple to manufacture and provides extended-release. Also there is a necessity for a process which is capable of imparting good flow and compressibility characteristics to the blend, solves the problem of capping and provides the desired extended-release as well.
- [16] The inventors have now discovered that an extended-release pharmaceutical composition of metformin, which maintains therapeutic blood level concentrations of the medicament in a patient for sufficiently long time, can be formulated as a monolithic matrix, which slowly releases the active agent over a prolonged period of time.

#### **Summary of the Invention**

- [17] According to one aspect, extended-release metformin tablets are formulated as a monolithic matrix comprising metformin, rate-controlling polymers and other pharmaceutically acceptable excipients.
- [18] According to yet another aspect, the extended-release metformin tablets are provided which can incorporate a high dose of metformin and are of acceptable size, making it convenient for oral administration.
- [19] In another aspect, the extended-release metformin tablet comprises a monolithic system that delivers highly soluble metformin at a relatively constant rate over extended periods of time, and is easy to manufacture.
- [20] According to yet another aspect, extended-release metformin tablets are provided which comprise 5-25% w/w of rate controlling polymers. The use of lesser amounts of rate controlling polymers than known for previous formulations ensures that the total weight of the dosage form is low and a single dosage unit is sufficient to provide the

therapeutic dosage of the drug. Thus, extended-release tablets provide benefits with respect to better patient convenience and patient compliance.

- [21] It is one of the aspects to provide extended-release metformin tablets which release metformin in a controlled manner over a time period of 24 hours, particularly over 12 hours.
- [22] According to yet another aspect, there is provided an extended-release metformin tablets of 850 mg strength comprising metformin, 5-25% w/w of rate-controlling polymers and other pharmaceutically acceptable excipients.
- [23] According to yet another aspect, there is provided an extended-release metformin tablets of 1000 mg strength comprising metformin, 5-25% w/w of rate-controlling polymers and other pharmaceutically acceptable excipients.
- [24] It is one general aspect to provide monolithic extended-release tablets comprising from about 500 mg to about 1000 mg metformin, wherein the total weight of the tablet does not exceed 1500 mg.
- [25] In another general aspect, a process is provided for preparing extended-release tablets of metformin or non-toxic acid addition salts thereof, which comprises blending of the ingredients followed by roller compaction or slugging. The compacts are suitably sized and compressed to form tablets.
- [26] In another general aspect, a process for preparing extended-release metformin tablets of 850 mg strength by roller compaction is provided.
- [27] In another general aspect, a process for preparing extended-release metformin tablets of 1000 mg strength by roller compaction is provided.
- [28] Roller compaction generally involves a screening procedure that can lead to a narrower particle size distribution with fewer particles at either extreme of the size range. Roller compaction provides several other advantages, for example, uniform blends are produced with uniform particle size range, flow properties are improved, aids in dust control, increases bulk density and controls particle hardness.
- [29] It is yet another aspect to provide extended-release metformin tablets, comprising:
  - [30] a. from about 500 mg to about 1000 mg metformin,
  - [31] b. 5-25% w/w rate-controlling polymer(s), and
  - [32] c. other pharmaceutically acceptable excipients.
- [33] According to another aspect, a process for preparing extended-release metformin tablets comprises:
  - [34] a. blending metformin, 5-25% w/w of rate controlling polymers and other pharmaceutically acceptable excipients,
  - [35] b. compacting / slugging,
  - [36] c. milling or crushing the compacted / slugged material of step (b) into granules, and
  - [37] d. lubricating and compressing the granules to form tablets.
- [38] According to our co-pending Indian patent application, 1002/DEL/2001 which is

incorporated herein by reference, metformin may be moisture conditioned before blending with rate controlling polymers and other excipients to further improve the flow properties. Alternatively, metformin may be blended with the rate controlling polymers and/or other excipients and then moisture-conditioned.

[39] Accordingly, a process for preparing extended-release metformin tablets comprises:

[40] a. moisture conditioning metformin,

[41] b. blending with 5-25% w/w of rate controlling polymers and other pharmaceutically acceptable excipients,

[42] c. compacting / slugging,

[43] d. milling or crushing the compacted / slugged material of step (b) into granules, and

[44] e. lubricating and compressing the granules to form tablets.

[45] Accordingly, another process for preparing extended-release metformin tablets comprises:

[46] a. blending metformin, 5-25% w/w of rate controlling polymers and other pharmaceutically acceptable excipients,

[47] b. moisture conditioning the blend,

[48] c. compacting / slugging,

[49] d. milling or crushing the compacted / slugged material of step (b) into granules, and

[50] e. lubricating and compressing the granules to form tablets.

[51] According to one of the embodiments, a process for preparing metformin extended-release tablets is provided, wherein the tablets have better strength, aesthetic appeal, desired profile and yield and are capable of incorporating very high doses of the drug, without making them unacceptably large to swallow.

[52] It is another aspect to provide a method for the treatment of non-insulin dependent diabetes mellitus in a patient in need thereof, comprising administering extended-release metformin tablets, comprising:

[53] a. from about 500 mg to about 1000 mg metformin,

[54] b. 5-25% w/w rate-controlling polymer(s), and

[55] c. other pharmaceutically acceptable excipients.

[56] The extended-release tablets may further include one or more of sulfonylureas, insulin, glitazones, alpha-glucosidase inhibitors, meglitinides, fibrates, statins, squalene synthesis inhibitors and angiotensin-converting enzyme inhibitors.

#### **Detailed Description of the Invention**

[57] Monolithic systems, composed of hydrophilic polymers and other excipients, for extended-release dosage forms are convenient and cost-effective.

[58] The term 'monolithic matrix' as described herein refers to a drug-containing matrix, formed by dispersing or dissolving the drug homogeneously in a suitable polymer. A monolithic matrix can be prepared by the direct compression, wet and dry granulation

methods. The diffusion of a drug through a matrix is the designed to be rate-limiting step in case of such dosage forms. The rate of release from such matrices typically follows a square root of time dependency. In monolithic preparations made of hydrophilic polymers, the drug release is governed by the swelling rate of the polymer matrix.

- [59] Metformin can be used in the form of acid addition salts of inorganic or organic acids. These acids are exemplified by, but are not limited to, acids such as hydrochloric acid, formic acid, acetic acid, malic acid, tartaric acid or fumaric acid.
- [60] Metformin can constitute up to 1000 mg per tablet.
- [61] Rate-controlling polymers may be selected from cellulose derivatives, starch or its derivatives, alginates, acrylic and methacrylic acid derivatives, polyethylene oxides, gums, carbohydrate based polymers and similar materials.
- [62] Cellulose derivatives may be selected from ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethylcellulose, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose of different degrees of substitution and molecular weights or similar materials. These polymers may be used alone or in combination.
- [63] The acrylic acid polymers may be carboxy vinyl polymers such as those available under the brand name Carbopol® (B.F. Goodrich, USA). Carbohydrate based polymers may be selected from xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum, locust bean gum and the like. Rate-controlling polymers constitute 5-25% w/w of the formulation.
- [64] The pharmaceutically acceptable excipients may be selected from diluents, binders, lubricants, glidants and flavouring agents which are physically and chemically compatible with metformin and which would help in optimizing tablet hardness, friability, drug dissolution and the production process.
- [65] Diluents may be selected from any such pharmaceutically acceptable excipients, which give bulk to the composition and improve compressibility. These may be selected from starch and starch derivatives, dicalcium phosphate, calcium sulphate, sorbitol, microcrystalline cellulose, lactose, glucose, mannitol, alginates, alkali earth metal salts, clay, polyethylene glycols or similar materials.
- [66] Binders may be selected from starch, mannitol, polyvinyl pyrrolidone, carboxymethyl cellulose, hydroxy alkyl celluloses, dextrin, carbohydrate gums, alginates, polyacrylic acid, polyvinylalcohol and similar materials or mixtures thereof.
- [67] Lubricants may be selected from talc, magnesium stearate, other alkali earth metal stearates like zinc, calcium stearate etc; sodium lauryl sulphate, hydrogenated vegetable oil, sodium benzoate, sodium stearyl fumarate, glyceryl monostearate, polyethylene glycol and similar materials.
- [68] Glidants may be selected from colloidal silicon dioxide, talc and similar materials.
- [69] The blend is compacted by roller compaction. Alternatively, this blend could be

compressed to make slugs. One of the embodiments includes compaction or slugging of metformin either alone or after blending with rate controlling polymers and/or with excipients.

[70] The compacted / slugged material is crushed / milled by a suitable milling machine like oscillating granulator / multimill / Fitzmill and sieved into the desired granule size.

[71] These granules are lubricated with the lubricant and compressed into tablets.

[72] If desired, metformin may be mixed with one or more other antidiabetic agents prior to the compaction step. Suitable antidiabetic agents include antidiabetic agents selected from the group consisting of sulfonylureas (e.g., glyburide, glipizide, glimepiride and gliclazide), a-glucosidase inhibitors (e.g., acarbose and miglitol); and glitazones (e.g., rosiglitazone and pioglitazone), as well as combinations of two or more of the foregoing antidiabetic agents.

[73] The following examples illustrate various embodiments and do not limit the claims in any manner.

[74] Example 1

[75]

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	1000.00
Sodium Carboxymethyl cellulose	25.00
Microcrystalline cellulose	85.00
Hydroxypropyl methyl cellulose	275.00
Magnesium stearate	3.75
Colloidal Silicon Dioxide	16.25
Water	45.00
<b>Total</b>	<b>1450.00</b>

[76] Process:

[77]

1. The ingredients were weighed and sifted through suitable sieves.
2. Metformin hydrochloride and microcrystalline cellulose were mixed in a blender and sprayed with required quantity of purified water.
3. The blend of step 2 was mixed with sodium carboxymethylcellulose, hydroxypropyl methyl cellulose, magnesium stearate and a part of colloidal silicon dioxide.
4. The mass of step 3 was sifted and then compacted using a roller compactor.
5. Compacted material was suitably sized.
6. Sized granules were lubricated and compressed into tablets.

[78]

Example 2

[79]

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	850.00
Sodium Carboxymethyl cellulose	21.25
Microcrystalline cellulose	72.25
Hydroxypropyl methyl cellulose	233.75
Magnesium stearate	3.1875
Colloidal Silicon Dioxide	13.8125
Water	38.25
<b>Total</b>	<b>1232.5</b>

[80] Process: As given for Example 1.

[81] The release profiles of tablets prepared according to Example 1 and 2 are provided in Table 1.

[82]

Table 1: Release profile of tablets of Example 1 and 2 in pH 6.8 phosphate buffer/900 ml/USP Apparatus II/50 rpm.

Time (hr)	Percent drug release (%) from tablets of Example 1	Percent drug release (%) from tablets of Example 2
0.5	23	21
1.0	33	30
2.0	46	45
4.0	63	66
6.0	76	79
8.0	85	87
10.0	91	95
12.0	94	96

[83] Example 3

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	1000.00
Sodium Carboxymethyl cellulose	25.00
Microcrystalline cellulose	36.50
Hydroxypropyl methyl cellulose	325.00

Magnesium stearate	3.00
Colloidal Silicon Dioxide	15.5
Water	45.00
<b>Total</b>	<b>1450.00</b>

[84] Process: As given for Example 1.

Example 4

[86]

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	1000.00
Dicalcium phosphate	205.00
Hydroxypropyl methyl cellulose	175.00
Magnesium stearate	5.00
Colloidal Silicon Dioxide	10.00
Talc	5.00
Water	20.00
<b>Total</b>	<b>1420.00</b>

[87] Process: As given for Example 1.

[88] The release profiles of tablets prepared according to Example 3 and 4 are provided in Table 2.

[89]

Tablet 2: Release profiles of tablets of Example 3 and 4 in pH 6.8 phosphate buffer/ 900 ml/USP Apparatus II/50 rpm.

Time (hr)	Per cent drug release (%) from tablets of Example 3	Per cent drug release (%) from tablets of Example 4
0.5	18	21
1.0	28	31
2.0	41	47
4.0	59	67
6.0	70	80
8.0	79	90
10.0	86	94
12.0	88	96

[90] Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, the invention is defined by the appended claims.